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(54) **SYSTEM AND METHOD FOR TESTING A BIOLOGICAL SAMPLE**

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(57) **ABSTRACT**

The method for testing a biological sample operates on a testing system. The testing system generally comprises an instrument that is configured to acquire data from a biological sample and a processor. In performing the method for testing, the instrument acquires data from the biological sample, and the processor compares the acquired data to predefined data criteria. Responsive to comparing the acquired data to the data criteria, the instrument may be adjusted, and another data set acquired. In one disclosed example of the testing system, a mass spectrometer acquires data from a biological sample. The acquired data is compared to predefined spectrum criteria. Responsive to the comparison, the mass spectrometer may be directed to resample the biological sample or proceed to another sample.

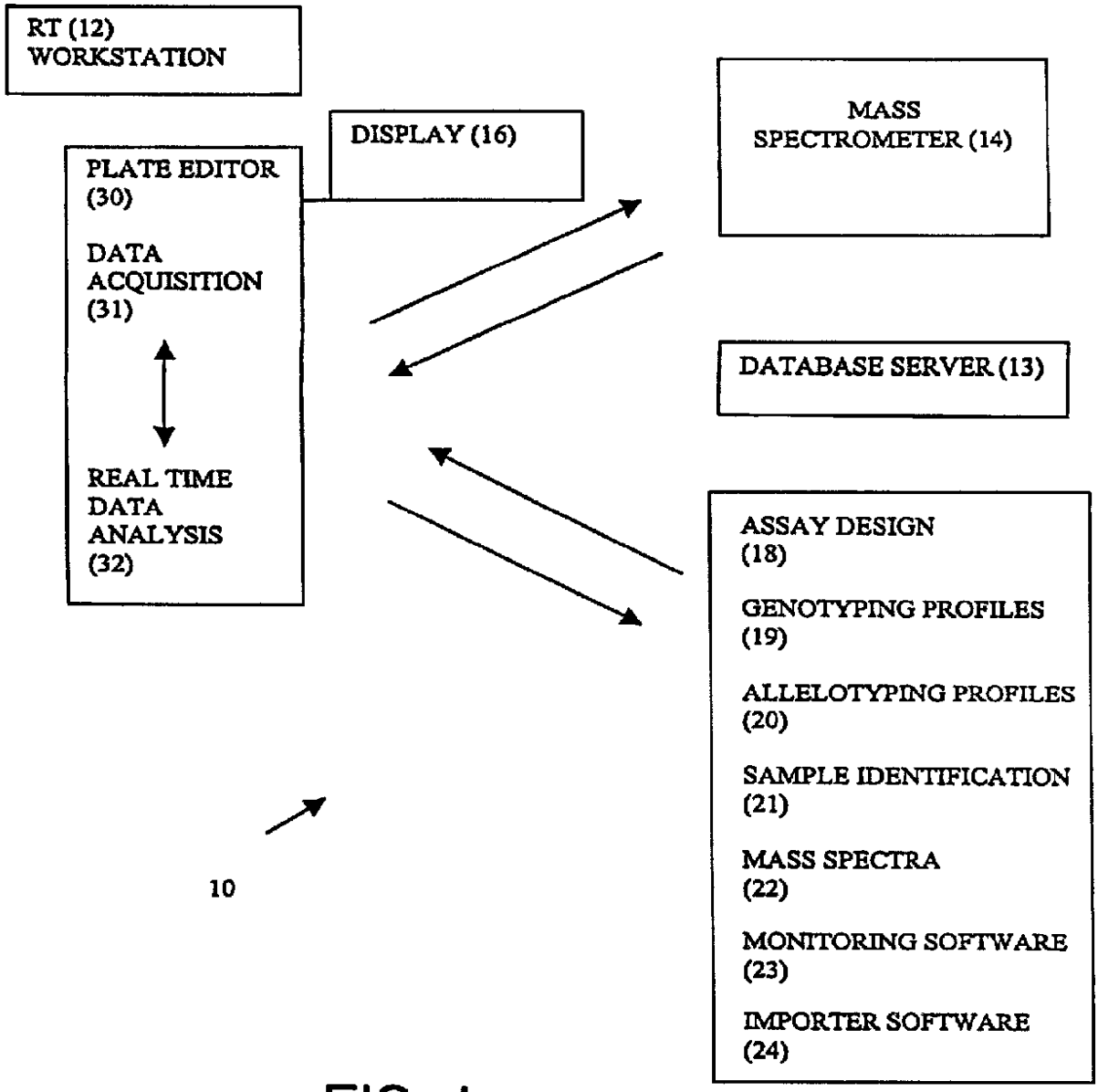
RT (12)
WORKSTATION
DISPLAY (16)
MASS
SPECTROMETER (14)
PLATE EDITOR
(30)
DATA
ACQUISITION
(31)
REAL TIME
DATA
ANALYSIS
(32)
DATABASE SERVER (13)
ASSAY DESIGN
(18)
GENOTYPING PROFILES
(19)
ALLELOTYPING PROFILES
(20)
SAMPLE IDENTIFICATION
(21)
MASS SPECTRA
(22)
MONITORING SOFTWARE
(23)
IMPORTER SOFTWARE
(24)
10

FIG. 1

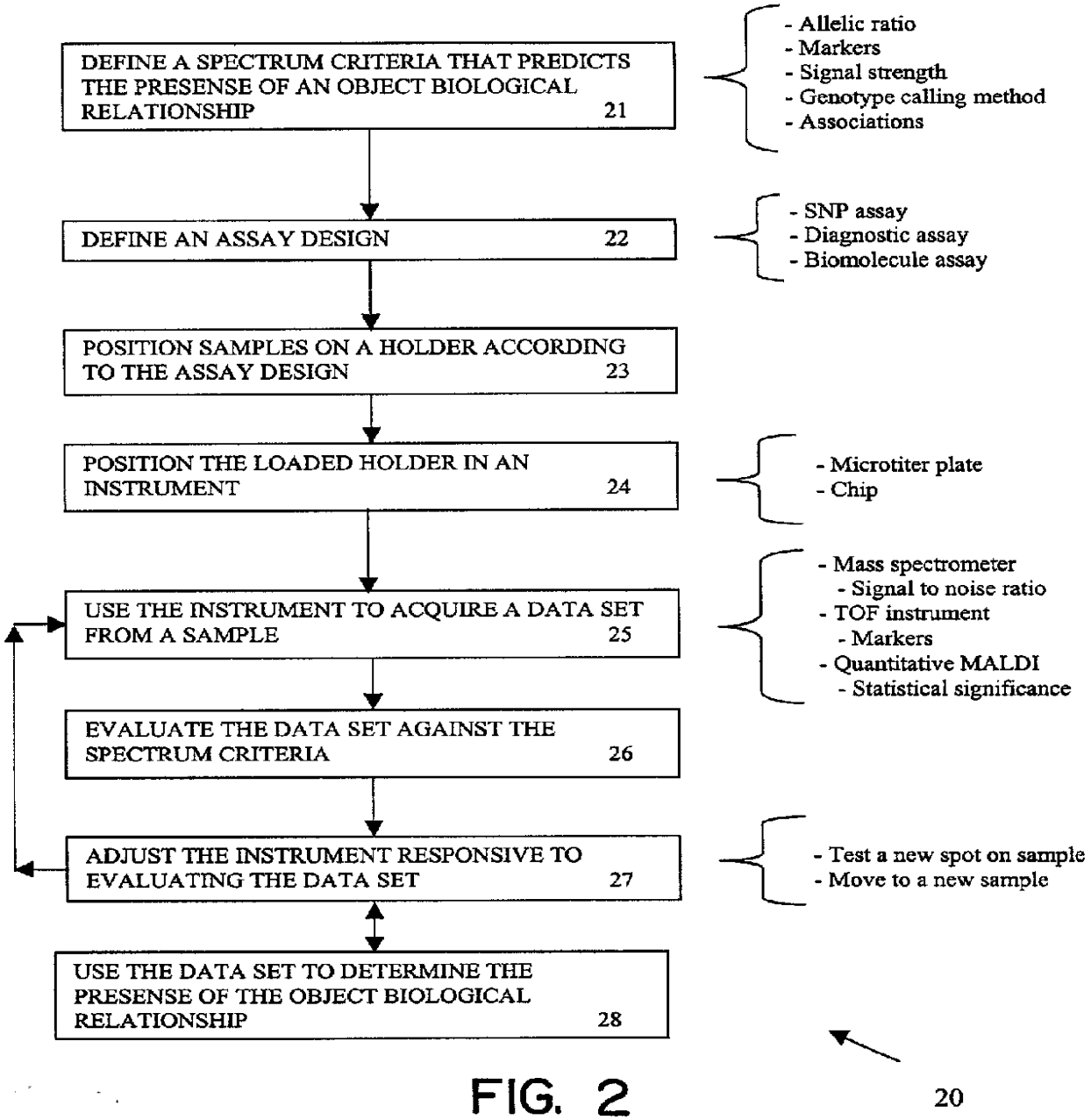
DEFINE A SPECTRUM CRITERIA THAT PREDICTS THE PRESENSE OF AN OBJECT BIOLOGICAL RELATIONSHIP 21
- Allelic ratio
- Markers
- Signal strength
- Genotype calling method
- Associations
DEFINE AN ASSAY DESIGN 22
- SNP assay
- Diagnostic assay
- Biomolecule assay
POSITION SAMPLES ON A HOLDER ACCORDING TO THE ASSAY DESIGN 23
POSITION THE LOADED HOLDER IN AN INSTRUMENT 24
- Microtiter plate
- Chip
USE THE INSTRUMENT TO ACQUIRE A DATA SET FROM A SAMPLE 25
- Mass spectrometer
- Signal to noise ratio
- TOF instrument
- Markers
- Quantitative MALDI
- Statistical significance
EVALUATE THE DATA SET AGAINST THE SPECTRUM CRITERIA 26
ADJUST THE INSTRUMENT RESPONSIVE TO EVALUATING THE DATA SET 27
- Test a new spot on sample
- Move to a new sample
USE THE DATA SET TO DETERMINE THE PRESENSE OF THE OBJECT BIOLOGICAL RELATIONSHIP 28
20

FIG. 2

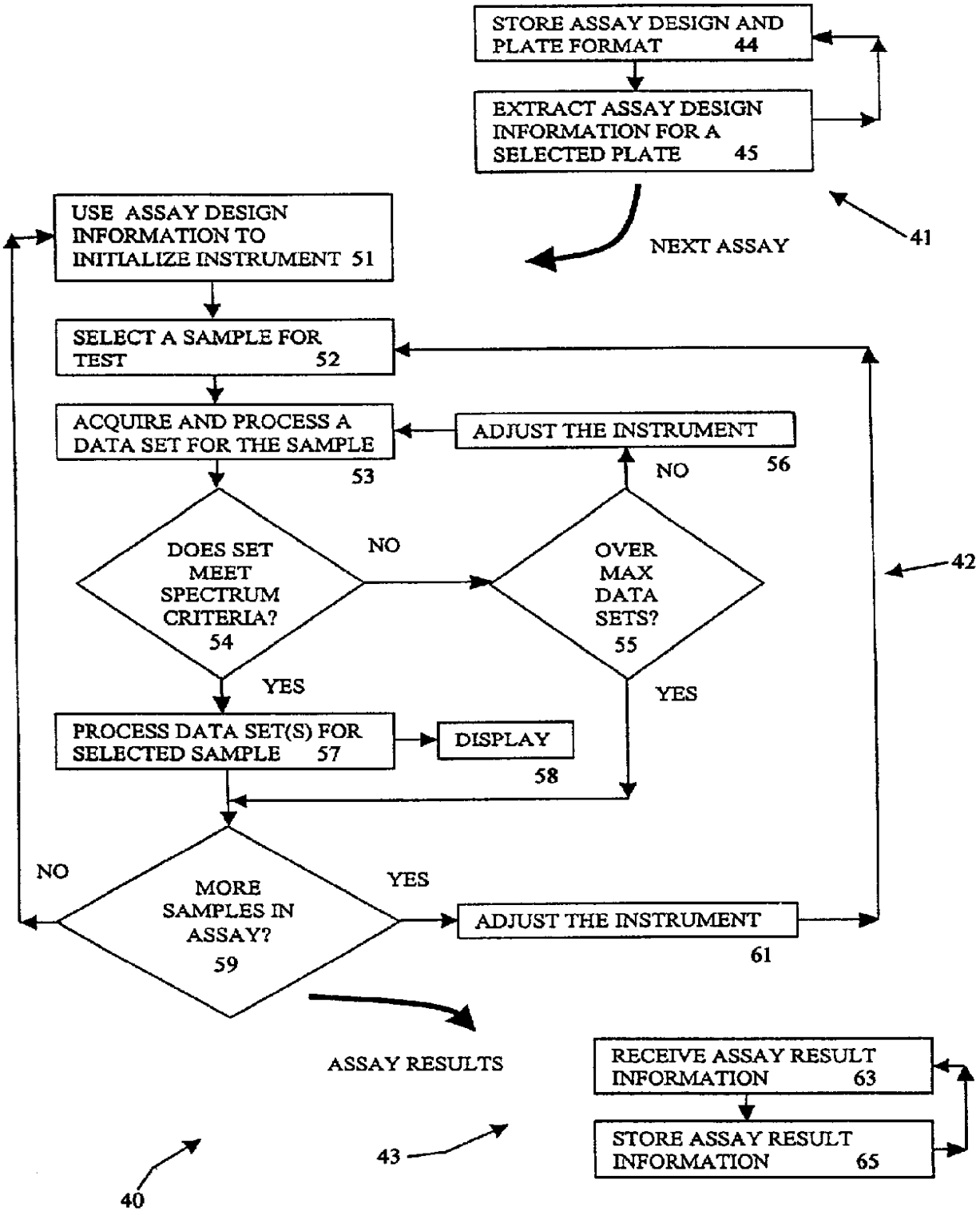
STORE ASSAY DESIGN AND PLATE FORMAT 44
EXTRACT ASSAY DESIGN INFORMATION FOR A SELECTED PLATE 45
NEXT ASSAY
41
USE ASSAY DESIGN INFORMATION TO INITIALIZE INSTRUMENT 51
SELECT A SAMPLE FOR TEST 52
ACQUIRE AND PROCESS A DATA SET FOR THE SAMPLE 53
ADJUST THE INSTRUMENT 56
NO
DOES SET MEET SPECTRUM CRITERIA? 54
NO
OVER MAX DATA SETS? 55
42
YES
YES
PROCESS DATA SET(S) FOR SELECTED SAMPLE 57
DISPLAY 58
NO
MORE SAMPLES IN ASSAY? 59
YES
ADJUST THE INSTRUMENT 61
ASSAY RESULTS
RECEIVE ASSAY RESULT INFORMATION 63
STORE ASSAY RESULT INFORMATION 65
43
40

FIG. 3

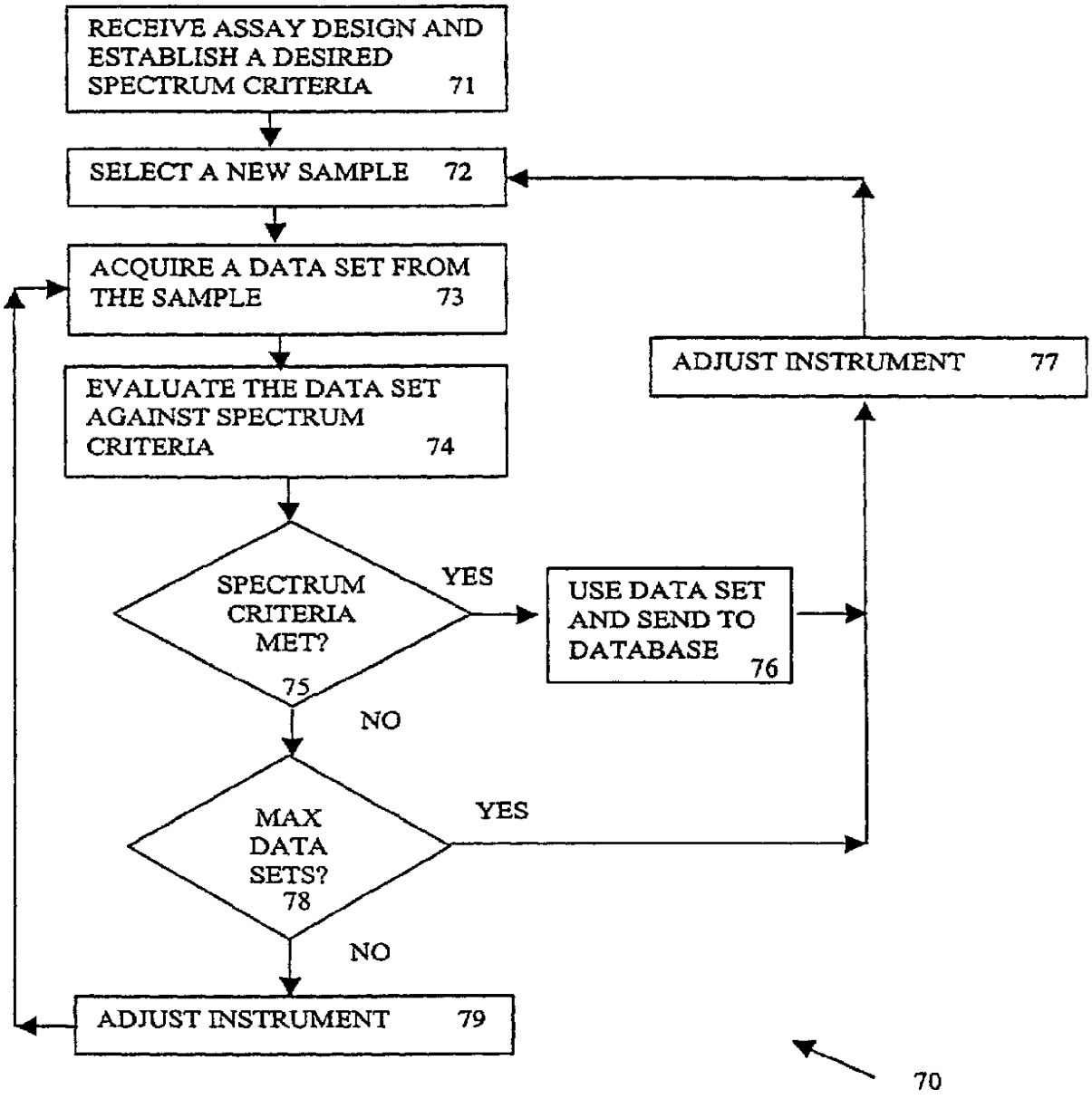
RECEIVE ASSAY DESIGN AND ESTABLISH A DESIRED SPECTRUM CRITERIA 71
SELECT A NEW SAMPLE 72
ACQUIRE A DATA SET FROM THE SAMPLE 73
EVALUATE THE DATA SET AGAINST SPECTRUM CRITERIA 74
SPECTRUM CRITERIA MET? 75
YES
USE DATA SET AND SEND TO DATABASE 76
ADJUST INSTRUMENT 77
NO
MAX DATA SETS? 78
YES
NO
ADJUST INSTRUMENT 79
70

FIG. 4

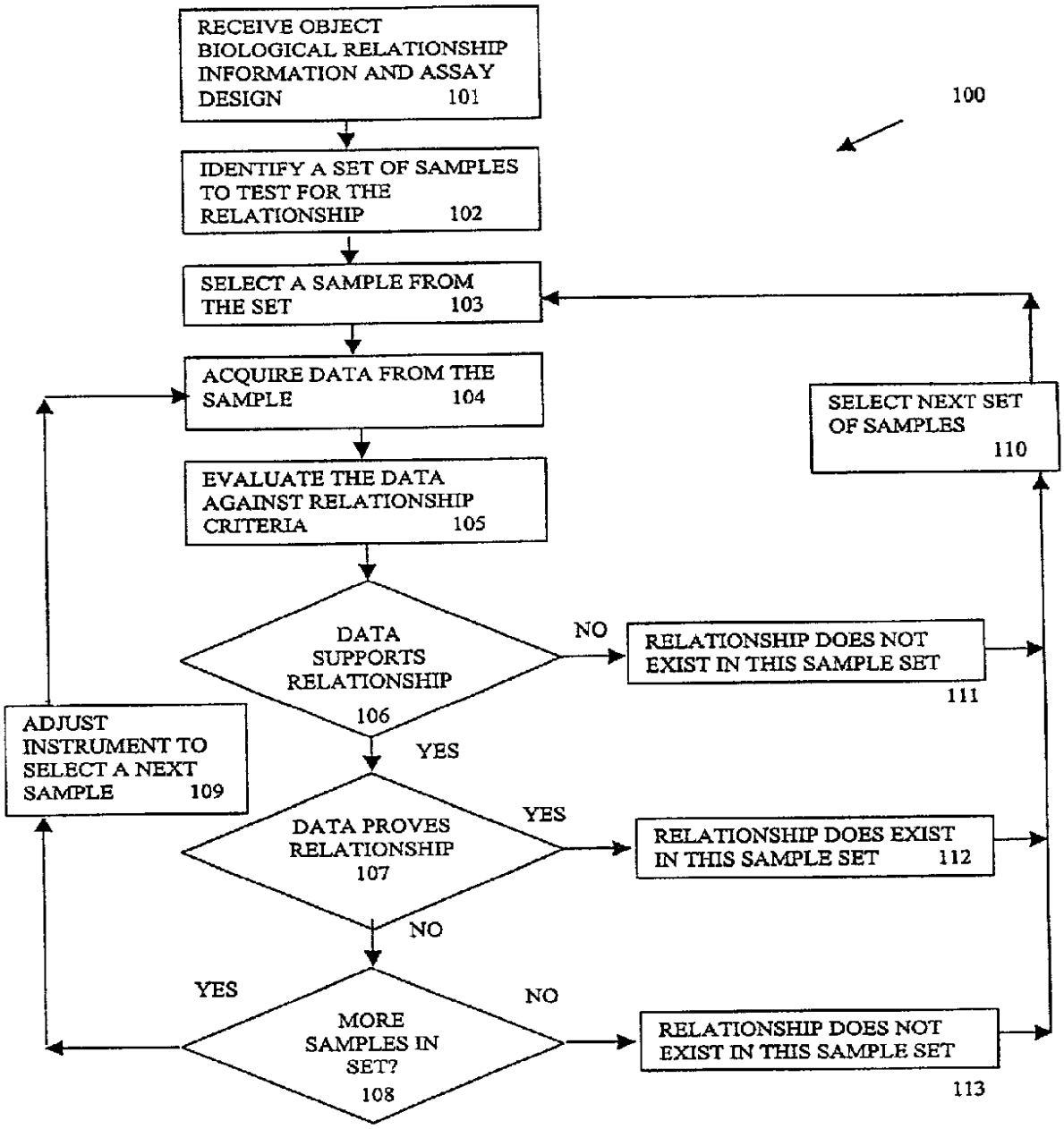
RECEIVE OBJECT BIOLOGICAL RELATIONSHIP INFORMATION AND ASSAY DESIGN 101
100
IDENTIFY A SET OF SAMPLES TO TEST FOR THE RELATIONSHIP 102
SELECT A SAMPLE FROM THE SET 103
ACQUIRE DATA FROM THE SAMPLE 104
SELECT NEXT SET OF SAMPLES 110
EVALUATE THE DATA AGAINST RELATIONSHIP CRITERIA 105
DATA SUPPORTS RELATIONSHIP 106
NO
RELATIONSHIP DOES NOT EXIST IN THIS SAMPLE SET 111
ADJUST INSTRUMENT TO SELECT A NEXT SAMPLE 109
YES
DATA PROVES RELATIONSHIP 107
YES
RELATIONSHIP DOES EXIST IN THIS SAMPLE SET 112
NO
YES
MORE SAMPLES IN SET? 108
NO
RELATIONSHIP DOES NOT EXIST IN THIS SAMPLE SET 113

FIG. 5

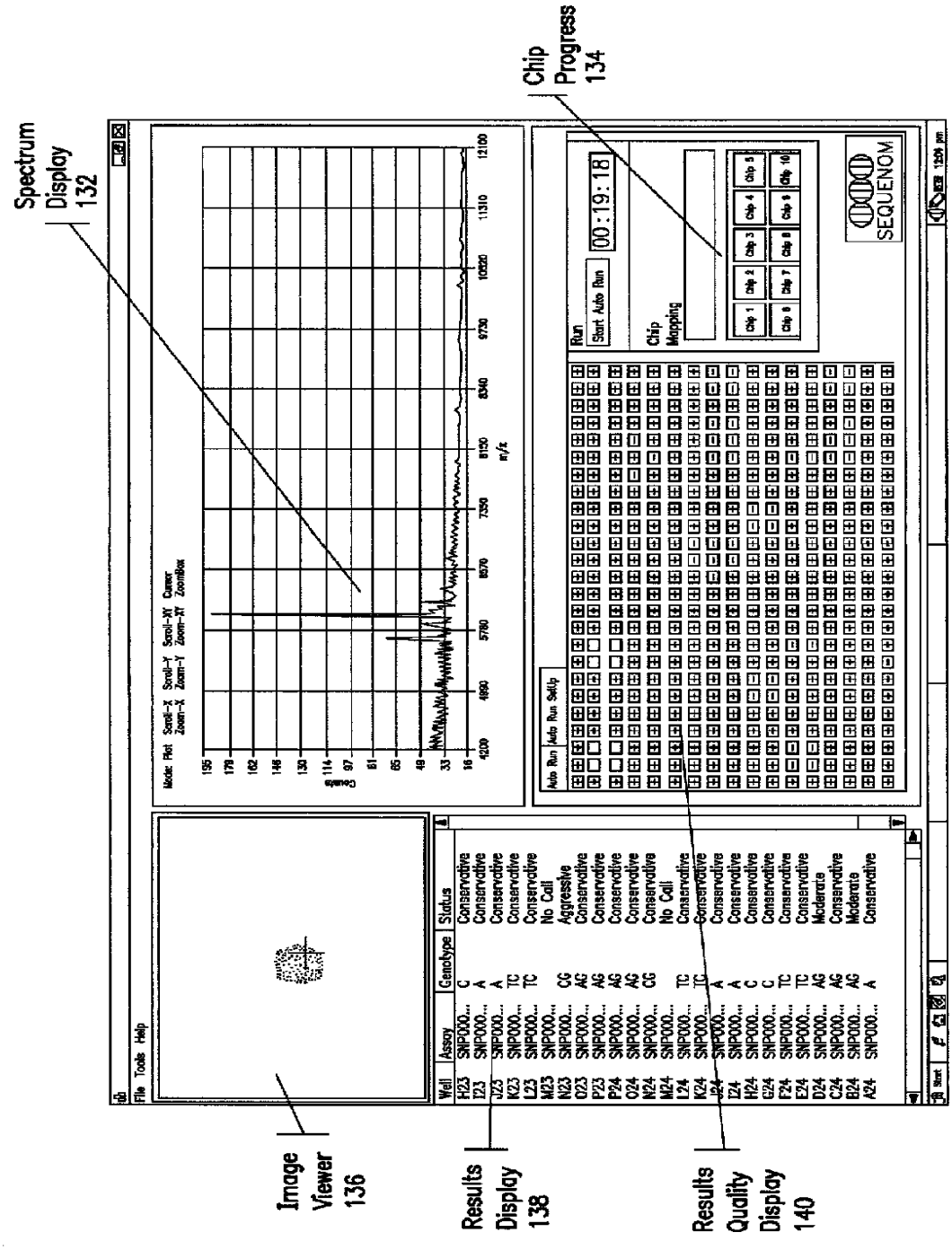
Spectrum Display 132
Chip Progress 134
Image Viewer 136
Results Display 138
Results Quality Display 140
130
File Tools Help
Mode: Plot Scroll-X Scroll-Y Scroll-XY Cursor
Zoom-X Zoom-Y Zoom-XY ZoomBox
Run
Start Auto Run
00:19:18
Chip Mapping
SEQUENOM
Auto Run Auto Run Setup
Well Assay Genotype Status
H23 SNP000... C Conservative
I23 SNP000... A Conservative
J23 SNP000... A Conservative
K23 SNP000... TC Conservative
L23 SNP000... TC Conservative
M23 SNP000... No Call
N23 SNP000... CG Aggressive
O23 SNP000... AG Conservative
P23 SNP000... AG Conservative
P24 SNP000... AG Conservative
O24 SNP000... AG Conservative
N24 SNP000... CG Conservative
M24 SNP000... No Call
L24 SNP000... TC Conservative
K24 SNP000... TC Conservative
J24 SNP000... A Conservative
I24 SNP000... A Conservative
H24 SNP000... C Conservative
G24 SNP000... C Conservative
F24 SNP000... TC Conservative
E24 SNP000... TC Conservative
D24 SNP000... AG Moderate
C24 SNP000... AG Conservative
B24 SNP000... AG Moderate
A24 SNP000... A Conservative

FIG. 6

SYSTEM AND METHOD FOR TESTING A BIOLOGICAL SAMPLE

TECHNICAL FIELD

[0001] The field of the present invention is testing methods for biological samples. In a particularly disclosed example, a system having a processor is used to implement the disclosed testing method.

BACKGROUND

[0002] Instruments, such as the mass spectrometer, are now routinely used to assist in identifying components of a biological sample. In particular, the MALDI time-of-flight (TOF) mass spectrometer has proven particularly useful in making biological determinations, such as genotyping or identifying single nucleotide polymorphisms.

[0003] The MALDI TOF mass spectrometer generally operates by directing an energy beam at a target spot on a biological sample. The energy beam disintegrates the biological material at the target spot, with the disintegrated component material being hurled toward a measurement module. The lighter component material arrives at the measurement module before the heavier component material. The measurement module captures the component material, and generates a data set indicative of the mass of the component material sensed. Typically, the data set is generated as a two dimensional spectrum, with the x-axis representing a mass number, and the y-axis representing a quantity number.

[0004] The data, which is often presented as a data spectrum, typically has peaks positioned on a generally exponentially decaying baseline. Each peak should ideally represent the presence of a component of the biological sample. Unfortunately, due to chemical and mechanical limitations, the data spectrum is replete with noise, so an accurate determination of biological components is challenging. Indeed, it takes an experienced operator to accurately read and interpret a data spectrum. However, the efforts of even the best trained human operator can suffer from inaccuracies and errors. Since the results derived from the data spectrum are often used in health care decisions, mistakes can be devastating. Therefore, operators are trained to make a determination only when certain of the result. In such a manner, a great number of tests result in no-calls, where the operator cannot clearly identify a data result.

[0005] Accordingly, the use of mass spectrometers risks an unacceptably large number of inaccurate calls if the operator is applying a rather loose standard to the data spectrum. Alternatively, the use of mass spectrometers becomes highly inefficient if the operator discards a large number of tests due to an inability to confidently make a call.

[0006] To assist the operator in making calls, the mass spectrometer may provide a level of data filtering. Typically, the data filtering attenuates a set magnitude of noise, thereby more conspicuously exposing valid peaks. However, such a filtering technique may actually mask important valid peaks, resulting in an incorrect analysis.

[0007] Modern trends in biotechnology are taxing the capabilities of instruments such as mass spectrometers and their operators. For example, mass spectrometers are now being used to identify single nucleotide polymorphisms (SNPs). However, SNPs may produce only slight peaks on the data spectrum, which are easily missed by an operator or buried in background noise. Further, mass spectrometers are also now being used for multiplexing, where multiple gene reactions may be present in a single sample. In such a manner, the resulting peaks may be smaller, more difficult to identify, and there may be more combinations of false readings. With such a complicated data spectrum, it is becoming more difficult for an operator to confidently determine if a valid peak exists for a particular genetic component.

[0008] The mass spectrometer, therefore, provides a data spectrum that is difficult for an operator to interpret. Even under the best of conditions, the operator is likely to either make identifications where the call should not have been made, or is likely to discard good acquired data because of perceived ambiguity. Accordingly, there exists a need for a more efficient and accurate method and system for identifying a biological sample.

SUMMARY OF THE INVENTION

[0009] It is therefore an object of the present invention to provide a testing system and method that overcomes the deficiencies in the prior art. It is also an object of the present invention to provide for efficient and accurate biological identification.

[0010] The method for testing a biological sample in accordance with the invention utilizes a testing system. The testing system generally comprises a processor and an instrument that is configured to acquire data from a biological sample. In performing the testing method, the instrument acquires data from the biological sample, and the processor compares the acquired data to predefined data criteria. Responsive to comparing the acquired data to the data criteria, the instrument may be adjusted, and another data set acquired. In one disclosed example of the testing system, a mass spectrometer acquires data from a biological sample. The acquired data is compared to predefined spectrum criteria. Responsive to the comparison, the mass spectrometer may be directed to resample the biological sample or proceed to another sample.

[0011] Advantageously, the disclosed method and system for testing a biological sample provides automated control of a mass spectrometer. More particularly, the new testing method enables a highly accurate determination of a biological sample with minimal manual intervention. Accordingly, biological samples may be identified and diagnostic tests performed with a degree of precision, speed, and accuracy not available from known testing systems.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **FIG. 1** is a block diagram of a testing system in accordance with the present invention;

[0013] **FIG. 2** is a flowchart of a testing process in accordance with the present invention;

[0014] **FIG. 3** is a flowchart of a testing process in accordance with the present invention that illustrates automated control of a testing instrument;

[0015] **FIG. 4** is a flowchart of a testing process in accordance with the present invention that illustrates oversampling a biological sample;

[0016] **FIG. 5** is a flowchart of a testing process in accordance with the present invention that illustrates acquiring data from multiple samples to establish the presence of a biological relationship; and

[0017] **FIG. 6** is an illustration of a computer display showing results from a testing system in accordance with the present invention.

DETAILED DESCRIPTION

[0018] Referring now to **FIG. 1**, an example testing system **10** for testing abilogical sample is illustrated. Generally, the testing system **10** contains a real time (RT) workstation **12** which includes a series of controllers that retrieve assay design parameters from the database server **13** and directs the acquisition and processing of data indicative of the biological sample from the mass spectrometer **14**. The processed data or genotyping results are then downloaded into a directory in the database server **13**.

[0019] With the testing system **10** generally disclosed, individual components will now be described. The testing system **10** has a RT workstation **12** that may be, for example, a computer system having storage and computational components, including one or more controllers. In a preferred embodiment, the RT workstation is made up of one controller **30** which acquires assay design specifications from the database server **13**, includes another controller **31** which automatically aligns the laser on the chip using an image system, controls the motor movement of the assay substrate at the mass spectrometer, and acquires the data signal directly from the mass spectrometer, and includes another controller **32** that communicates with the controller **31** by receiving a data signal and providing instruction for additional data acquisition. Additional data acquisition may be dependent on the quality of the data previously obtained. The data is preferably stored on a local hard drive of the RT workstation **12** until the results from all the samples are compiled. The compiled data is stored in a directory in the database server **13**. The RT workstation **12** preferably has a display **16** for visually communicating test results and status information. In a preferred embodiment, the RT workstation **12** is a computer, such as an IBM compatible personal computer system, communicating with the mass spectrometer using a known communication standard, such as a parallel or serial interface. It will be appreciated that the workstation and controllers may be alternatively embodied. For example, the RT workstation **12** may be integral to the mass spectrometer **14** or another system component, or the workstation and controller **12** may be placed at a remote location from the mass spectrometer. In such a manner the network topography, such as a wide area network or a local area network, would provide a communication path between the mass spectrometer **14** and the RT workstation **12**. Although the RT workstation **12** is preferably a standalone computer device, it will be appreciated that one or more of the controllers may be, for example, a microprocessor or other programmable circuit device capable of performing a programmed process.

[0020] The mass spectrometer **14** is preferably a MALDI Time-of-Flight (TOF) instrument. Such a device is more fully described in co-pending U.S. patent application Ser. No. 09/663,968, filed Sep. 19, 2000 and entitled, "SNP Detection Method", and U.S. patent application Ser. No. 09/285,481, filed Apr. 5, 1999 and entitled, "Automated Process Line", both of which are incorporated herein by reference in their entirety. The mass spectrometer **14** is configured with an interface to communicate with the workstation controller **12**. The interface preferably conforms to a known data communication standard, for ease of connection. Although a single interface may enable the controller **12** to both receive data from the mass spectrometer **14** and send instructions to the mass spectrometer **14**, two or more separate interfaces may be used. Although the preferred test system **10** incorporates a MALDI TOF mass spectrometer, it will be appreciated that other types of analytical instruments may be used.

[0021] The testing system **10** may provide the database server **13** with one or more databases, such as database **18**, database **19**, database **20**, database **21** and database **22** stored in direct access storage devices. It will be appreciated that other forms of data storage may be used. However, a structured database provides a convenient format for storing and retrieving data. In a preferred embodiment one of the databases, such as database **18**, stores assay design information, a database **19** stores genotyping profiles, a database **20** stores allelotyping profiles, database **21** stores sample identification information, while the other database **22** stores test results for later analysis. It will be appreciated that fewer or more databases may be used to store assay and test information. The database server **13** may also contain one or more controllers such as controller **23** and controller **24**. In a preferred embodiment the controller **23** monitors the data acquisition of the individual samples on the assay substrate or chip. Once the data is received from all samples in the assay, the data monitoring controller **23** downloads all or part of the assay information and stores the information in a directory in the test results database **22**. The controller **24** imports the data into a directory in the results database **22**.

[0022] The RT workstation **12** has sufficient processing ability to extract assay design information from the assay design database **18**, and to convert the assay design information into a format for providing specific directions to the mass spectrometer **14**. For example, the controller may access the database **18** and request a specific assay design. The specific assay may be set up to provide a microtiter plate with hundreds, or even thousands, of samples on each plate. The test may require that samples be tested in a specific order, and based upon the result from previous tests, the order may be adjusted, or some samples may even be eliminated from the assay. The RT workstation receives the assay design information and converts the assay design information into commands for the mass spectrometer **14**. Upon starting the assay, the RT workstation **12** sends initialization commands to the mass spectrometer **14** consistent with the assay design.

[0023] Extracting an assay design from a database and generating mass spectrometer commands may be a time consuming and processor intensive operation. It would be particularly undesirable for the extraction process to interfere with the more real-time control of the mass spectrometer. Accordingly, it is preferred that the RT workstation **12** perform a database extraction process, and database storage functions, as background tasks, or at a time when such tasks will not materially interfere with the more real-time control of the mass spectrometer **14**. As used herein, real-time control refers to the ability of the RT workstation **12** to

receive data from the mass spectrometer **14**, process the data, and provide command direction to the mass spectrometer in an automated and efficient manner.

[0024] The RT workstation **12** defines physical map of the biological samples on the assay plate or chip by manual input of the information by the operator or an automated scanning system such as a bar code reader.

[0025] A mass spectrometer **14** receives the biological sample for analysis and generates an electrical data signal representative of genotype information associated with the sample tested under direction from the real time workstation **12**. The instrument is initialized when it is provided with specific data acquisition parameters, either manually or in a default mode. The acquisition parameters may include the number of laser shots per spot, the maximum number of raster per sample, and voltage, delay time, calibration constants and other parameters that will be well-known to those skilled in the art. The mass spectrometer is initialized according to test assay parameters, and acquires data indicative of the biological samples. More particularly, the data acquired by the mass spectrometer is typically in the form of an electronic data spectrum. The electronic data spectrum can be retrieved by the RT workstation.

[0026] Biological samples are analyzed when the RT workstation **12** directs the automatic alignment of the mass spectrometer laser on assay surface or chip using an imaging system and controls movement of the laser from sample to sample and assay surface to assay surface when multiple assay surfaces or chips are held in a multi-component holder.

[0027] Biological or genotyping information is acquired directly from the mass spectrometer **14** by the RT workstation **12**. The signal is converted into amass data spectrum by the RT workstation **12** where a genotype is determined. If the sample genotype cannot be called, the RT workstation **12** will recognize the situation and may direct an adjustment to the mass spectrometer **14**. For example, if the acquired spectrum has an unacceptably high signal to noise ratio, the workstation controller **12** may direct the mass spectrometer **14** to test the same sample again, but may adjust the mass spectrometer **14** to direct its beam at a different spot on the sample, or may select alternative power settings or measurement filters. In another example, the controller **12** may direct the mass spectrometer **14** to take a series of data sets from the same sample until the standard deviation in the aggregate results achieves a desired degree of certainty. It should be understood that, even though the same sample may be tested multiple times, each test will be taken from a unique spot on the sample.

[0028] Referring now to **FIG. 2, a** method of testing a biological sample is shown. The method of testing first predefines spectrum criteria that predicts the presence of a biological relationship in block **21**. The predefined spectrum criteria will vary depending on the assay being run. For example, the spectrum criteria may be set to assure a minimum allelic ratio is exceeded. In this regard, the spectrum criteria may be set to reject acquired data where the allelic ratio is below a threshold, such as 5%. In another example, the presence of specific markers may be required to validate acquired data. In another example, the spectrum criteria may require that a peak exceed a signal to noise figure before accepting the acquired data as valid. Further, statistical methods may be applied to the acquired data, or sets of acquired data, to determine if a particular peak is statistically signification. Using such a statistical method may dramatically increase the accuracy of calling the composition of a biological sample. U.S. application Ser. No. 09/663,968 filed Sep. 19, 2000 teaches a specific example of a statistical method as applied to acquired spectrum data. It will be appreciated that the spectrum criteria can be defined in numerous ways consistent with the teaching of this application.

[0029] With the spectrum criteria predefined, block **22** shows that the assay design is defined, and then preferably stored in a database for use in controlling the instrument. In a preferred embodiment, the instrument is a MALDI TOF mass spectrometer. It will be appreciated that other instruments may be substituted. The defined assay design is used to generate the initial settings for the instrument, and then is further used to direct the instrument during the assay test.

[0030] Biological samples are then positioned in block **23** for test in the instrument. The samples are positioned preferably on a holder such as a microtiter plate. It will be appreciated that other types of holders, such as test tubes or chips, may be substituted for a microtiter plate holder. Although it is more convenient to place all samples for one assay on a single holder, samples for a single assay may be placed on multiple holders.

[0031] The holder is positioned in the instrument, as indicated in block **24**. The holder may be manually positioned, or may be positioned under robotic control. If the holder is robotically controlled, then information extracted from the assay design may be used to direct the robotic control to place the proper holder in the instrument. If manually positioned, a visual display may be used to assist the human operator in identifying and verifying the proper holder.

[0032] Blocks **25-28** represent the real time control of the instrument and will be described further below. This real time control enables the automated and efficient operation of the instrument, and provides accuracies and repeatabilities in test results that are not available in known systems.

[0033] In block **25**, the instrument acquires a data set from a biological sample. In a preferred embodiment, the acquired data is in the form of an acquired data spectrum. In the exemplary system described in the '968 Application, the data set is generated by first finding height of each peak, then extrapolating noise profile, and finding noise of each peak, next calculating signal to noise ration, and finding residual error, and calculating and adjusting signal to noise ratio, and developing a probability profile, and determining peak probabilities, and determining allelic penalty, and adjusting peak probability by allelic penalty, and calculating genotype probabilities, and testing ratio of genotype probabilities.

[0034] The acquired data is evaluated in block **26**. In a preferred embodiment, the acquired data is compared against the spectrum criteria previously defined. As described above, this comparison can be, for example, a comparison of peak strength, peak position, markers, s/n ratio, allelic ratio, or a statistical calculation. Further, the comparison may be multi-dimensional, for example, requiring first that a particular marker be located and then testing that an appropriate signal to noise ratio exists. It will also be appreciated that the comparison step may use data from

multiple acquired data sets, for example, to calculate the standard deviation for the group. Accordingly, the comparison will compare the standard deviation in the group of data sets to determine if the results should be derived from the newly acquired data.

[0035] Responsive to the comparison, the workstation controller adjusts the instrument in block **27**. For example, if the signal to noise ratio was too low in a first data set, the instrument may be adjusted to test the same sample, but at a different spot on the sample. By moving to a new target spot, new data may be acquired for the same sample. In testing the new spot, it is quite possible that different or better analytical results may be found. Thus, taking a reading at a second spot may enable making an analytical call on a sample when it was not possible with only a single spot test. Further, testing additional spots on an individual sample may permit the calculation of aggregate results with a lower error rate than relying solely on a single test spot. By automating the evaluation of the acquired data and control of the instrument, the overall assay test can be manipulated to provide a requisite level of accuracy and tolerance. Accordingly, the maximum number of samples can be accurately called for a particular assay, but yet time and system resources are not wasted by testing more spots than necessary.

[0036] After the instrument is adjusted and set to acquire a next data set, the method returns to block **25** to acquire the next data set. As described above, the next data set may be for the same sample, or the instrument may have been adjusted to the next sample. After testing is completed, processing moves to block **28**.

[0037] Block **28** shows that the results from the acquired data are analyzed to determine the presence of an object biological relationship. For example, the assay may be attempting to locate particular single nucleotide polymorphisms (SNPs), or may be allele typing, or may be genotyping. Irrespective of the particular biological relationship searched for, the relative success of the search may be used by the **FIG. 2** testing method in directing further data acquisitions. For example, if in a multiple sample assay, the biological relationship is ruled out after only the first sample, then the method can be directed to skip testing the rest of the samples in the assay and move on. In another example, if after testing multiple samples for a particular assay the results are still ambiguous, block **28** can be used to determine if the ambiguity can be removed by increasing the certainty of the results for a particular sample. If so, the test can be directed by the workstation to automatically take additional data acquisitions and attempt to salvage the assay. Without such an automated and intelligent process, the assay would be rejected. Accordingly, the **FIG. 2** testing method provides a higher level of calls, and a higher level of call certainty than with known testing methods.

[0038] Referring now to **FIG. 3**, another method of testing a biological sample is shown. The **FIG. 3** testing method **40** generally has a control loop **42**, an initialization loop **41**, and a results loop **43**. The control loop **42** is responsible for acquiring data sets, comparing the data sets to predefined spectrum criteria, and adjusting the instrument responsive to the evaluation of the acquired data. In this regard, the control loop must operate efficiently enough to permit the timely operation of the overall test system. Therefore, certain of the setup and storage functions have been off-loaded to the background loops **41** and **43**. It will be appreciated that more or less functionality may be placed in the background loops to accommodate different response times needed in the control loop **42**.

[0039] The initialization loop **41** is a background loop that permits storage of assay design and plate information in block **44**. Preferably, the assay design and plate information is stored in a database form. Preferably, the database of assay design and plate information may be used by multiple test systems, and may be accessed remotely. In such a manner a remote researcher may define an assay in a single database, and that newly defined assay may be operated on multiple test systems.

[0040] Since extracting and converting the assay information into control information is a time consuming process, the extraction process is performed in block **45**. Of course, it will be appreciated that as typical computer workstation computational powers increase, it may be desirable to have the extraction process made a part of the control loop **42**. Since the extracting step is preferably a background step, the extraction process may be performed for a next assay while the control loop **42** is actively performing an assay. Thus, when the control loop has finished an assay, the extracted information from block **45** may be sent to block **51** to start the control loop **42** for a next assay.

[0041] The information from block **45** is received in block **51**, where the information is used to initialize the instrument. In a preferred embodiment, the instrument is a MALDI TOF mass spectrometer. The initialization commands may include identifying the first sample to test, the proper power settings, and the desired filtering for the data.

[0042] A sample is selected for test in block **52**, and data is acquired from the test sample in block **53**. The acquired data may be sufficiently processed to determine target characteristics for the acquired data. For example, if signal to noise ratio is an important indication of test quality, then a signal to noise ratio may be calculated for the acquired data. More particularly, the acquired data will be processed to facilitate comparison with predefined spectrum criteria.

[0043] The predefined spectrum criteria, as previously discussed, define the analytical characteristics for good data. In block **54**, the acquired data is compared to the predefined spectrum criteria. If the acquired data is good, a "YES" outcome at block **54**, then the acquired data is further processed in block **57** to extract biological information, and the data is formatted and displayed in block **58**. However, if the acquired data is not good, a "NO" outcome at block **54**, then block **55** asks if the maximum number of spots have been shot for this sample. For example, a typical mass spectrometer can take a maximum of about 15 to 20 shots on any given sample. To assure the integrity of the test, it may be advisable to set the maximum to a safe number, such as 10. The sample is not further processed if the maximum shots have been exceeded. Thus, if less than 10 spots have been shot, a "NO" outcome at block **55**, then the instrument is adjusted to a new spot in block **56**, and data is acquired on the new spot in block **53**. In block **54**, the newly acquired data is compared to the spectrum criteria. Alternatively, block **54** can use aggregated data from multiple test spots to determine if the aggregated data is good.

[0044] Once a sample has been judged good or bad, then block **59** asks if there are more samples in the assay. If so,

a "YES" outcome at block **59**, then the instrument is adjusted in block **61** to shoot the next sample. If all the samples have been tested, a "NO" outcome at block **59**, then the control loop **42** resets and a next assay is initiated.

[0045] When the control loop **42** is complete, then the results from the assay are passed to the background results loop **43**. The results loop **43** may perform additional post processing on the data in block **63**, which may include a manual review of the results. The data and results may then be stored in block **65**. Preferably, the data and results are stored in a database that is accessible from remote locations so a remote researcher or other test operators may review the results.

[0046] Referring now to **FIG. 4**, another testing method **70** is illustrated. The testing method **70** allows an assay designer to establish a minimum standard for each biological sample in block **71**. More particularly, the testing method **70** is directed to increasing the confidence in the results from each sample. As discussed above, a typical mass spectrometer can take a data set from multiple spots on a single biological sample. The testing method **70** enables the test to dramatically increase the confidence for each sample, while minimizing the number of testing samples that must be acquired.

[0047] In the testing method **70**, a biological sample is selected in block **72**, and a data set is acquired in block **73**. In block **74**, the acquired data is evaluated against the data criteria set for the sample. For example, the data criteria may expect a signal to noise ratio to exceed a floor value. In this regard, each data set acquired for a particular sample is compared against the data criteria. Alternatively, data collected from multiple shots in the same sample may be used in the comparison. For example, the data criteria may require that the standard deviation between spots on the same sample not exceed a particular value. Thus the comparison step could include determining the standard deviation for all spots in the single sample to determine if confidence is sufficiently high to call the sample. It will be appreciated that the comparison step may entail a wide range of analytical and algorithmic calculations, either on individual data sets or aggregates of data sets.

[0048] Importantly, the testing method **70** permits setting the data criteria in a manner that minimizes the number of data acquisitions. For example, the data criteria could be accept a sample when a single data set has a signal to noise ratio meeting one level, or meeting a lower level for aggregate data sets. Thus, a single strong reading would be sufficiently robust, and multiple shots would not be needed on that sample. In a similar manner, the comparison could be set to accept sample data if the standard deviation between two successive shots is less than 5%, or accept the data if the standard deviation is less than 7% for 3 shots, or less than 10% for 4 or more shots. Such flexible data criteria permit the assay designer to set a high degree of confidence with a minimum of data readings. Accordingly, the test system **70** operates at high degree of efficiency and accuracy as compared to known systems.

[0049] Once the data criteria have been met, a "YES" outcome at block **75**, the results are stored in block **76**, preferably in a database, and the instrument adjusted to move to the next sample in block **77**. Accordingly, a new sample is selected in block **72**.

[0050] If the data criteria have not yet been met, a "NO" outcome at block **75**, then block **78** asks if there are any remaining spots on the sample. If unshot spots exist, a "NO" outcome at block **78**, the instrument is adjusted in block **79** to acquire data from a new spot, and the data is acquired in block **73**. If the data criteria are not met, and there are no unshot spots, a "YES" outcome at block **78**, then that particular sample is rejected, and the test moves on to a new sample.

[0051] Referring now to **FIG. 5**, a diagnostic testing method **100** is disclosed. The diagnostic testing method is directed to finding a relationship among a set of samples that proves a particular biological relationship exists. For example, certain clinical diagnostics may look at multiple samples from an individual before identifying that the individual is at risk for a particular disease. The diagnostic testing method enables such a clinical diagnosis at a level of certainty and a level of efficiency not available in known systems.

[0052] The diagnostic testing method **100** receives an assay design and relationship criteria at block **101**. The relationship criteria define the range of values and certainties where a relationship can be identified. In a preferred embodiment, the relationship is the likelihood that a particular individual will contact a particular disease. Due to the seriousness of the identification, it is crucial that such an identification be made only under the most confident conditions. Accordingly, known systems have required redundancies and over-testing to build confidence sufficient to make such a drastic announcement regarding an individual's health.

[0053] In block **102**, a set of samples is identified for testing for the relationship. As there are likely several, even tens of samples to test, it is also likely that the set of samples may be present on multiple holders. Thus the testing method **100** should account for instructing an operator or a robot to deliver and load different holders as needed.

[0054] A particular sample is selected from the set in block **103**, and data acquired from the sample in block **104**. The acquired data is evaluated against the relationship criteria in block **105**. In a preferred embodiment, testing system **100** incorporates aspects of previously discussed testing system **70** to increase the confidence that the results from an individual sample are robust. The previously discussed method of over-sampling a single biological sample can dramatically increase the confidence in the data from a single sample.

[0055] In block **106**, the acquired data is evaluated to determine if it supports the object relationship. If the data does not support the object relationship, a "NO" outcome, then it is reported that the relationship does not exist in the set in block **111**, and the test moves on to the next set of samples in block **110**. Due to the high degree of confidence in sample results, it is possible for the testing method **100** to reject the entire sample and move to the next set. Accordingly, the testing method **100** may operate efficiently.

[0056] If block **106** finds that the data does support the relationship, a "YES" outcome, then block **107** asks if the data acquired thus far conclusively proves the relationship exists. If enough data has been collected, and the relationship proved, a "YES" outcome at block **107**, then block **112**

reports that the relationship exists, and the test moves on to the next set of samples. Thus, the testing method **100** only takes the necessary number of data acquisitions to call a diagnosis, enabling efficient operation.

[**0057**] If block **107** finds that the collected data does not prove the biological relationship, a "NO" outcome, then block **108** asks if there are any more samples to be tested in the sample set. If no more samples exist, a "NO" outcome at block **108**, then block **113** reports that the relationship could not be proved, and the test moves on to the next sample set. If there are more samples to be tested, then the instrument is adjusted to the next sample in block **109**, and data acquired from the new sample in block **104**.

[**0058**] **FIG. 6** shows an example user display **130** for a test system. The user display **130** is preferably presented on a computer monitor connected to an IBM compatible computer system. In a preferred embodiment, the user display **130** is presented using a Microsoft® Windows® compatible display program.

[**0059**] The user display **130** has a spectrum window **132** for displaying a data spectrum of the most recently acquired data set. The spectrum window **132** enables an operator to watch, in near real-time, the data being collected by the instrument. If multiple spots are shot for a particular sample, each successive data spectrum may be displayed in a different color so variations between spots is easily identified.

[**0060**] The user display also has a holder representation **134**. The holder representation of **FIG. 6** shows individual sample wells in a microtiter plate. For example, a well representation shows the wells in a physical microtiter plate holder. As each well is tested, the well representation turns a different color base on whether the sample was accepted or rejected. A results display **138** shows assay data and a results quality display **140** shows run data for data sets. Accordingly, as the test progresses, an operator may identify certain systemic problems. For example, if all wells in a particular column fail, then there may be a problem with the syringe used to fill that particular column.

[**0061**] The user interface **130** also has a sample view **136** which shows a live image of the sample currently being tested. With this view, an operator may visually identify spots that have been used within a particular sample. Also, the operator may be able to identify certain systemic problems, such as a too small sample being deposited into certain wells.

What is claimed is:

1. A system for performing a biological assay, comprising:

an instrument configured to acquire biological data from a biological sample; and

a processor that communicates with the instrument, such that the processor

directs the instrument to acquire data indicative of the biological sample,

establishes a data spectrum criteria,

generates data parameters using the acquired data,

compares the data parameters to the spectrum criteria,

adjusts the instrument responsive to evaluating the data, and

directs the instrument to acquire other data for the biological assay.

2. The system according to claim 1 wherein the processor further performs the step of receiving an assay design.

3. The system according to claim 1 further including a database in communication with the processor, wherein the database holds assay information.

4. The system according to claim 3 wherein the processor further performs the steps of:

receiving a portion of the assay information from the database; and

using the received portion of the assay information to adjust the instrument.

5. The system according to claim 1 where the instrument is configured as a mass spectrometer.

6. The system according to claim 1 where the processor is configured as a computer device coupled to the instrument.

7. The system according to claim 1 where the processor is configured as a computer device in the instrument.

8. The system according to claim 1 wherein the step of generating the data parameters includes generating a data parameter indicative of standard deviation.

9. The system according to claim 1 wherein the processor generates the data parameters by generating a data parameter indicative of statistical probability.

10. The system according to claim 1 wherein the processor generates the data parameters by generating a data parameter indicative of allele probability.

11. A system for testing a biological sample, comprising:

an instrument configured to acquire biological data from the biological sample;

a processor communicating to the instrument, the processor performing steps comprising:

directing the instrument to acquire data indicative of the biological sample;

evaluating the acquired data;

adjusting automatically the instrument responsive to evaluating the data; and

directing the instrument to acquire other data indicative of the biological sample.

12. The system for testing a biological sample according to claim 11 wherein the processor further performs the steps comprising:

establishing a spectral criteria; and

evaluating the acquired data using the spectral criteria.

13. A system for performing a diagnostic assay using a set of biological samples, comprising:

an instrument configured to acquire biological data from the biological samples;

a processor communicating to the instrument, the processor performing the steps comprising:

directing the instrument to acquire data indicative of one of the biological samples in the set;

evaluating the acquired data;

determining if the acquired data supports a diagnostic conclusion; and

directing the instrument to acquire data indicative of a next one of the biological samples in the set responsive to the determining step.

14. A system for performing a diagnostic assay using a set of biological samples, the system comprising:

a workstation that communicates with an instrument that is configured to acquire biological data from successive biological samples in the set, and that controls the instrument to acquire data indicative of each successive biological sample, determines if the instrument should be adjusted in response to evaluating the acquired data from a set, and directs the instrument to acquire other data indicative of the biological sample responsive to the determination; and

a database server that stores the acquired data from the biological samples.

15. The system according to claim 14, wherein the workstation evaluates the acquired data, determines if the acquired data supports a diagnostic conclusion, and directs the instrument to acquire data indicative of a next one of the biological samples in the set, responsive to the determination.

16. The system according to claim 14, wherein the workstation includes an assay design controller that acquires assay design specifications from the database server.

17. The system according to claim 14, wherein the workstation includes an alignment controller that automatically aligns a laser of the instrument on one of the biological samples and controls movement of the sample in the instrument so as to receive biological data from the instrument.

18. The system according to claim 17, wherein the workstation includes a data controller that receives a data signal from the alignment controller and makes the determination of directing the instrument to acquire other data indicative of the biological sample, in response to the determination.

19. The system according to claim 14, wherein the workstation is constructed integrally with the instrument.

20. A method of performing a diagnostic assay using a set of biological samples, the method comprising:

directing an instrument to acquire data indicative of one of the biological samples in the set;

evaluating the acquired data;

determining if the acquired data supports a diagnostic conclusion; and

directing the instrument to acquire data indicative of a next one of the biological samples in the set responsive to the determination.

21. The method according to claim 20, further comprising:

establishing a data spectrum criteria;

generating data parameters using the acquired data;

comparing the data parameters to the spectrum criteria, and

adjusting the instrument responsive to evaluating the data.

22. The method according to claim 21, wherein generating the data parameters includes generating a data parameter indicative of standard deviation.

23. The method according to claim 21, wherein generating the data parameters includes generating a data parameter indicative of statistical probability.

24. The method according to claim 21, wherein generating the data parameters includes generating a data parameter indicative of allele probability.

25. The method according to claim 21, further including receiving an assay design.

26. The method according to claim 21, further including storing the acquired data from the biological samples of the set in a database server.

27. The method according to claim 26, further including:

receiving a portion of the assay information from the database server; and

using the received portion of the assay information to adjust the instrument.

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